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EXAMINER
EINSMANN, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/766,399	Applicant(s) BRUCE ET AL.	
	Examiner Juliet C Einsmann	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 10/10/02, paper number 11. Claims 2, 7, 8, 12, and 16 have been amended and claims 1, 17, and 18 have been canceled. Claims 2-16 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

2. Applicant is advised that should claim 7 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plant promoters comprising synthetic multimeric promoter element regions (SMPER) consisting of instant SEQ ID NO: 65, 66, 67, 65, 68, 69, 71, 72, and 70, does a SMPER that comprises the promoter elements recited in the claims sequentially with intervening

sequences or SMPER sequences that are modified from the recited sequence identifiers within the bounds of hybridization language or homology language recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 2 is drawn to an isolated plant promoter that comprises a series of promoter elements sequentially present in the promoter, but allows for there to be intervening sequences between the elements (part a). Part (b) of Claim 2 particularly recites that the promoter comprises instant SEQ ID NO: 65, part (c) recites a nucleotide sequence of not less than 50 nucleotides that hybridizes under stringent conditions to (a) or (b), and part (d) recites a polynucleotide which has at least 90% sequence identity to (a) or (b). Part (c) of claim 2 recites hybridization conditions which are included in stringent hybridization conditions, but this language is non-limiting because while these hybridization conditions are included in stringent conditions, so are any other hybridization conditions. Claims 4-6 depend from claim 2 and recite chimeric genes, transformation vectors and plants. Claim 7 is drawn to a plant or plant part having stably incorporated into its genome a DNA construct comprising a plant promoter operably linked to a coding sequence, wherein the plant promoter is a plant promoter of claim 2. Claim 8 recites a plant or plant part having stably incorporated into its genome a DNA construct comprising a plant promoter operably linked to a coding sequence, wherein the plant promoter comprises a nucleotide sequence of the same scope as those described in claim 2. Claims 9-11 depend from claim 2 and further limit the species of the plants. Claim 12 is drawn to plant cells having stably incorporated into its genome a DNA construct comprising a plant promoter operably linked to a coding sequence, wherein the plant promoter comprises a nucleotide

sequence of the same scope as those described in claim 2. Claims 13-15 depend from claim 12. Claim 16 depends from claim 2 and is a method for expressing a heterologous nucleotide sequence in a plant using a promoter as claimed in claim 2.

The specification teaches that certain promoter elements have strong binding activity with maize nuclear extracts (Example 1). The specification teaches that these elements were randomly combined to make promoters, and that 17 were tested in experiments where maize was transformed with a construct comprising the promoters (Examples 3-4). The experiments demonstrated that of the 17 SMPER promoters tested, nine resulted in the promotion of LUC activity in transgenic maize. The promoter herein disclosed as SEQ ID NO: 65 is one of the nine promoters that demonstrated activity in maize.

The prior art teaches many constructs for the expression of heterologous genes in plants. Many of these fall within the scope of the broad definition of SMPER provided in the specification, and to the extent that the prior art falls within the scope of the instant claims, the claims are enabled for that scope. This rejection is particularly applied to the rejected claims to address claims which require the elements recited in claim 2(a) with any possible intervening sequences and sequences that hybridize or have 90% homology to 2(a) or 2(b) .

The ability of a promoter to function is highly sequence specific. The art teaches repeatedly that mutations in a critical region of a promoter element can destroy the ability of a construct to function in promotion. For example, Pietrzkowski *et al.* (Experimental Cell Research, 193, 283-290 (1991)) teaches that when synthetic promoters were produced wherein the sequence of an enhancer element was mutated, little to no promotion was observed from the constructs where the promoter was mutated (see for example Figure 6). Chan *et al.* (Plant

Molecular Biology 46 :131-141, (2001)) mutation in a critical XXIII element of the GAPB promoter abolished transcription completely (Figure 6), while mutations in other elements did not abolish activity (Figure 6). Thus, it is evident that it is highly unpredictable how promoter elements will respond to even very minor sequences changes. In addition, the order that promoter elements occur in a construct has an effect on the functionality of the promoter. Omilli *et al.* (Molecular and Cellular Biology, June 1986, p. 1875-1885) teach that the relative arrangement of promoter elements is a critical factor contributing to the activity of the promoter (ABSTRACT, for example).

The specification underscores this unpredictability by demonstrating that of 17 SMPER constructs produced, only nine of them were able to promote expression of a marker gene in maize. And even similar promoters containing similar numbers of elements, for example A56 and A51 which have the same number of elements, do not have the same response. That is, A51 was able induce LUC activity, while A56 was not. There is no clear pattern as to which sets of elements work or how to predict on its face if a set of elements will be able to promote expression.

With regard to the claimed and elected invention, there is only a single working example in a genus that contains hundreds of millions of possible promoter constructs which have been modified by any number of deletions, insertions, order changes, and rearrangements, that working example being a promoter comprising SEQ ID NO: 65. With regard to claim 2(a), while the claim requires the presence of particular elements in a particular order, it allows for an undefined number of intervening sequences, and further, part 2(c) does not require that all of the elements be present or that they all be in any particular order. The specification does not provide

any guidance as to how the elements can be rearranged from the order of SEQ ID NO: 65 and still result in a functional promoter, nor does the specification provide any guidance as to what number of intervening sequences can be placed between the recited elements and still result in a functional promoter. With regard to the elements of the claims that allow for sequences that "hybridize to" or the recited promoters and elements, such claims encompass promoters comprising elements that are modified from the elements taught in the instant specification. However, the specification does not provide any examples of such sequence, nor does the specification particularly teach how the elements in the promoter of claim 2(b) can be modified and still retain its ability to promote transcription. In light of the sequence specificity required for promoter activity, and the high degree of unpredictability with regard to the ability to change the sequence of a promoter element and have it retain its functionality, such guidance would be necessary to one to make and use the claimed invention.

The practice of the claimed invention commensurate in scope with the claims would require the construction and screening of hundreds of millions of possible promoters that comprise the elements recited in claim 2(a) with any intervening sequences, in any order, or that hybridize to those elements or that have homology with those elements. The construction and screening of all of these possible promoters to determine the functional promoters would require undue experimentation because there is absolutely no way to predict which promoters would be functional in light of the high level of sequence specificity in promoter sequences.

Thus, in light of the broad scope of the claims, the high level of unpredictability in the promoter art, the lack of examples and direction provided in the specification, and the high level of experimentation necessary to practice the claimed invention, it is concluded that undue

experimentation is necessary to practice the claimed invention commensurate in scope with the instant claims.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 2-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishige *et al.* (EP 0754757 A2).

Ishige *et al.* teach a plant having stably incorporated into its genome a DNA construct comprising a plant promoter operably linked to a coding sequence, said plant promoter comprising at least one synthetic multimeric promoter element region (SMPER) that enhances expression of said coding sequence (Examples 4, 5, and 6, page 6). The promoters used by Ishige *et al.* meet the definition of a SMPER provided in the specification because they contain more than one promoter element in an arrangement not found in nature (see specification, page 4, lines 24-27). For example, the construct called Gbox10/-90/GUS have a "Gbox" element linked to the minimal region of the cauliflower mosaic virus 35S promoter.

This reference is applied to claims 2-16 insofar as they are drawn to include "a nucleotide sequence of not less than that hybridizes under stringent conditions" to the nucleotide sequence of (a) or (b). The teachings of Ishige *et al.* meet the limitations of these claims. The promoters taught by Ishige et al. are more than 50 nucleotides. The promoters taught by Ishige

et al. all contain the minimal region of the cauliflower mosaic virus 35S promoter, which is taught in SEQ ID NO: 3 of the disclosure of Ishige *et al.* The promoter element disclosed herein and called "AS-1" is identical to nucleotides 4-31 of the sequence taught by Ishige *et al.* as SEQ ID NO: 3. Thus, the promoters taught by Ishige *et al.* are constructs that comprise at least one synthetic multimeric promoter element region having a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of (a) or (b). The promoters taught by Ishige *et al.* meet the limitations of claim 2 because they comprise elements that would hybridize under stringent conditions to the instantly disclosed and claimed promoter of section (a) or (b). The hybridization conditions recited in claim 1 (and the other independent claims) are nto limiting to the claims, because the claims merely designate that these are included in stringent conditions, but leaves open the interpretation of other hybridization conditions as "stringent conditions." Every hybridization condition is stringent, whether it be a high level of stringency or a low level of stringency. Furthermore, Ishige *et al.* teach a chimeric gene comprising the promoter operably linked to a coding sequence (GUS), an expression cassette, a transformation vector, and plants stably transformed with the transformation vector. Ishige *et al.* exemplify a dicot plant and a monocot plant (tobacco and rice), and further teach that the methods and vectors of their invention can be used with a wide variety of plants, including maize (p. 4, line 31).

Response to Remarks

The rejections set forth herein have been modified to address the amendments to the claims set forth in paper number 11.

Applicant cites portions of the specification that are asserted to provide guidance for variants and identification of sequences resulting from site-directed mutagenesis that would encompass all sequences with at least about 90% identity to SEQ ID NO: 65, and as providing information suitable for isolating sequences, their variants and the mutations (page 12 of the specification). Applicant also asserts that methods for introducing mutations and variants are well known to those of skill in the art. However, neither the guidance cited in the specification, nor the methods for introducing mutations that are "well known to those in the art" provide specific guidance as to how instant SEQ ID NO: 65 can be modified yet still retain its ability to function as a promoter. It is established in the rejection and in the art that the modification of promoters without resulting in the loss of ability to function is highly unpredictable, and thus, significant guidance would be required in the specification in order to enable promoters, constructs comprising such promoters, or methods of using promoters that are modified in sequence from the particular functional promoters provided in the specification.

Applicant cites Genentech, Inc, v. NovoNordisk as supporting their claim of enabling disclosure, providing a quotation from the Federal Circuit's decision (p. 8). However, the analysis provided in this case supports the examiner's rejection of the claims. In this case, a method for using cleavable fusion expression to make hGH was found to lack enabling support from the specification. The patent in question provided general guidance as to how to use cleavable fusion expression to make hGH, but "not describe in any detail whatsoever how to make hGH using cleavable fusion expression. For example, no reaction conditions for the steps needed to produce hGH are provided; no description of any specific cleavable conjugate protein appears." This is similar to the instant application which provides general guidance and relies on

the teachings of the prior art to suggest that modified versions of instant SEQ ID NO: 56 can be provided which are functional promoters without undue experimentation. In the Genentech case, the court goes on to state,

> "Genentech's arguments, focused almost exclusively on the level of skill in the art, ignore the essence of the enablement requirement. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable... However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research."

The instant specification provides vague ideas as to how to modify the seven functional promoters that are provided, but no specific guidance as to how to modify any one of them and still produce functional promoters. With regard to modified versions of SEQ ID NO: 56, those changed by adding intervening sequences between elements, by changing the order of elements (encompassed by hybridization language) or by changing particular portions of the nucleotide sequences, this specification provides only a starting point, not specific guidance as to how to modify the disclosed sequence.

Applicants argue that while the methods require selection of promoter exhibiting the desired activity, that this selection is routine. However, with regard to the hundreds of thousands of possibilities encompassed in the instant claims, applicants have not provided any guidance which overcomes the unpredictability of the area of technology of making promoters, as has been discussed in the rejection and in the previous remarks.

Applicant argues that the Ishige promoter is not capable of hybridizing under stringent conditions with the polynucleotides of claim 2, 8, or 12, particularly listing the hybridization

conditions 50% formamide, 1M NaCl, 1% SDS at 37°C, and a wash in 0.1XSSC at 60-65°C). However, the limitation where stringent conditions are so defined is not present in the claims. The claims merely designate that these are included in stringent conditions, but leaves open the interpretation of other hybridization conditions as "stringent conditions." Every hybridization condition is stringent, whether it be a high level of stringency or a low level of stringency. Amendment of the claims to say "wherein stringent conditions are..." would obviate the art rejections.

Conclusion

7. A plant promoter comprising a synthetic multimeric promoter element region that comprises instant SEQ ID NO: 65 is free of the prior art. A claim so limited would be allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Einsmann
Examiner
Art Unit 1634

December 23, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600